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☐ 1. Document ID: US 6143874 A

L4: Entry 1 of 3

File: USPT

Nov 7, 2000

US-PAT-NO: 6143874

DOCUMENT-IDENTIFIER: US 6143874 A

TITLE: Antibodies to the neurotrophic factor NNT-1

DATE-ISSUED: November 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chang; Ming-shi	Newbury Park	CA		

US-CL-CURRENT: 530/387.9; 424/130.1, 424/139.1, 424/141.1, 424/145.1, 530/387.1, 530/388.1, 530/388.24

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	INOC	Draw Desc	Image
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☐ 2. Document ID: US 6054294 A

L4: Entry 2 of 3

File: USPT

Apr 25, 2000

US-PAT-NO: 6054294

DOCUMENT-IDENTIFIER: US 6054294 A

TITLE: Nucleic acid molecules encoding the neurotrophic factor NNT-1

DATE-ISSUED: April 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chang; Ming-shi	Newbury Park	CA		

US-CL-CURRENT: 435/69.1; 435/252.3, 435/254.11, 435/320.1, 435/325, 536/23.51

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	INOC	Draw Desc	Image
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☐ 3. Document ID: US 5741772 A

L4: Entry 3 of 3

File: USPT

Apr 21, 1998

US-PAT-NO: 5741772

DOCUMENT-IDENTIFIER: US 5741772 A

TITLE: Neurotrophic factor NNT-1

DATE-ISSUED: April 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chang; Ming-shi	Newbury Park	CA		

US-CL-CURRENT: 514/2; 530/300, 530/350

Full	Title	Claim	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	EWAC	Draw Desc	Image
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L3 and (NNT-1)

3

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NEWS 8 Mar 22 TRCTHERMO no longer available
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and USPATFULL
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=> s treatment
L1 6724316 TREATMENT

=> s l1 and IgE
L2 14811 L1 AND IGE

=> s l1 and neurotrophin 1
L3 12 L1 AND NEUROTROPHIN 1

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PROCESSING COMPLETED FOR L3
L4 4 DUP REMOVE L3 (8 DUPLICATES REMOVED)

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L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
2001:565111 Document No. 135:147766 Preparation of scsCNTFR/NNT-1 fusion proteins and their therapeutic use. Elson, Greg; Gauchat, Jean-francois (Pierre Fabre Medicament, Fr.). PCT Int. Appl. WO 2001055219 A2 20010802, 78 pp. DESIGNATED STATES: W: AU, BR, CA, CN, JP, MX, US, ZA; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (French). CODEN: PIXXD2. APPLICATION: WO 2001-FR254 20010126. PRIORITY: FR 2000-1035 20000127; FR 2000-13090 20001012.

AB The invention concerns a scsCNTFR/NNT-1 fusion protein comprising a NNT-1 protein, a scNTFR.alpha. protein and a binding element which binds said two proteins. The invention also concerns a compn. comprising said fusion protein as medicine for preventing and/or treating neurodegenerative diseases such as amyotrophic lateral sclerosis, Parkinson's disease or Huntington's disease, for maintaining muscle mass in paralyzed persons, for treating obesity or cancer. Methods for prepg. the fusion proteins are also specifically claimed.

L4 ANSWER 2 OF 4 MEDLINE
1998226804 Document Number: 98226804. PubMed ID: 9560265. Targeted expression of a multifunctional chimeric neurotrophin in the lesioned sciatic nerve accelerates regeneration of sensory and motor axons. Funakoshi H; Risling M; Carlstedt T; Lendahl U; Timmusk T; Metsis M; Yamamoto Y; Ibanez C F. (Department of Neuroscience, Karolinska Institute, 171 77 Stockholm, Sweden.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Apr 28) 95 (9) 5269-74. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Peripheral nerve injury markedly regulates expression of neurotrophins and their receptors in the lesioned nerve. However, the role of endogenously

produced neurotrophins in the process of nerve regeneration is unclear. Expression of a multifunctional neurotrophin, pan-**neurotrophin-1** (PNT-1), was targeted to the peripheral nerves of transgenic mice by using a gene promoter that is specifically activated after nerve lesion but that is otherwise silent in all other tissues and during development. PNT-1 is a chimeric neurotrophin that combines the active sites of the neurotrophins nerve growth factor, brain-derived neurotrophic factor, and neurotrophin-3 and binds and activates all known neurotrophin receptors. In adult transgenic mice, PNT-1 was highly expressed in transected but not in intact sciatic nerve. Morphometric analyses at the electron microscopy level showed increased and accelerated recovery of axon diameter of myelinated fibers in crushed peripheral nerves of transgenic mice compared with wild type. Examination of nerve bundles in target tissues indicated accelerated reinnervation of foot pad dermis and flexor plantaris muscle in transgenic mice. Moreover, transected sensory and motor axons of transgenic mice showed faster and increased return of neurophysiological responses, suggesting an accelerated rate of axonal elongation. Importantly, transgenic mice also showed a markedly ameliorated loss of skeletal muscle weight, indicating functional regeneration of motor axons. Together, these data provide evidence, at both the anatomical and functional levels, that neurotrophins endogenously produced by the lesioned nerve are capable of significantly accelerating the regeneration of both sensory and motor axons after peripheral nerve damage. In addition, our results indicate that exogenous PNT-1 administration may be an effective therapeutic **treatment** of peripheral nerve injuries.

- L4 ANSWER 3 OF 4 MEDLINE
 95132649 Document Number: 95132649. PubMed ID: 7831338. Pan-**neurotrophin 1**: a genetically engineered neurotrophic factor displaying multiple specificities in peripheral neurons in vitro and in vivo. Ilag L L; Curtis R; Glass D; Funakoshi H; Tobkes N J; Ryan T E; Acheson A; Lindsay R M; Persson H; Yancopoulos G D; +. (Department of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Jan 17) 92 (2) 607-11. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
- AB Pan-**neurotrophin 1** (PNT-1) is a synthetic trophic factor engineered by combining active domains of the neurotrophins nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin 3 (NT-3) into an NT-3 backbone. This molecule was produced in transiently transfected COS cells or in baculovirus-infected insect cells transfected COS cells or in baculovirus-infected insect cells and subsequently purified to homogeneity. Saturation binding in embryonic spinal sensory neurons demonstrated a greater number of high-affinity binding sites for PNT-1 than for its parental molecule NT-3. PNT-1 was shown to efficiently block the chemical crosslinking of NGF, BDNF, and NT-3 to their cognate Trk receptors and to the low-affinity NGF receptor expressed on neuronal and nonneuronal cells. PNT-1 stimulated survival and proliferation of MG87 fibroblasts expressing either TrkA, TrkB, or TrkC. PNT-1 also promoted survival of a greater number of embryonic dorsal root ganglion neurons than any of the other neurotrophins alone, and its effects were equivalent to a combination of NGF, BDNF, and NT-3. Analysis of receptor-specific neurotrophic activities demonstrated that PNT-1 efficiently rescued TrkA mRNA-containing sympathetic neurons and TrkB and TrkC mRNA-containing sensory neurons from the dorsal root and nodose ganglia. Finally, PNT-1 showed robust retrograde transport to DRG neurons in vivo after injection into the sciatic nerve. Radiolabeled PNT-1 accumulated in small-, medium-, and large-sized neurons. Coinjection with different unlabeled neurotrophins inhibited PNT-1 transport in distinct subpopulations of neurons of different sizes, suggesting that this molecule affects sensory neurons of different modalities. These results indicate that PNT-1 is a potent and multispecific neurotrophic factor that

may be useful in the **treatment** of peripheral neuropathies and nerve damage.

L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS

1994:622997 Document No. 121:222997 Neurotrophic factors with activities derived from nerve growth factor, brain-derived neurotrophic factor and neurotrophins that efficiently activate receptor tyrosine kinases. Ibanez, Carlos Fernando Moliner; Persson, Haakan Bengt (McIntyre, Katherine Rowe, USA). PCT Int. Appl. WO 9412539 A1 19940609, 69 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US11292 19931119. PRIORITY: US 1992-979630 19921120.

AB Chimeric neurotrophins with the activities of multiple parental neurotrophins are described for use in the **treatment** and diagnosis of neurol. disorders. The proteins are manufd. by expression of the cloned gene. A series of analogs in which the variable domains of NGF and BDNF were exchanged were used to identify the sequences important for activation of receptor protein tyrosine kinases. The data from these expts. were used to design a multifunctional neurotrophin agonist (Pan-**Neurotrophin-1**, PNT-1) that was based on NT-3 with the N-terminal domain of NGF and the region V variable region of BDNF. The protein was able to stimulate the efficient phosphorylation of receptor tyrosine kinases TrkA, TrkB, and TrkC with the factor showing binding to all three kinases. The chimeric factor was able to stimulate neurite outgrowth from explanted sympathetic ganglia and was effective in promoting the survival of nodose neurons (45% survival).

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 17:46:41 ON 08 MAY 2002

L1 6724316 S TREATMENT
L2 14811 S L1 AND IGE
L3 12 S L1 AND NEUROTROPHIN 1
L4 4 DUP REMOVE L3 (8 DUPLICATES REMOVED)

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=> s 13 and neurotrophin 1 antagonist

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L6 0 S L3 AND NEUROTROPHIN 1 ANTAGONIST

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=> s l2 and B cell stimulating factor 3
2 FILES SEARCHED...

L8 0 L2 AND B CELL STIMULATING FACTOR 3

=> s l2 and inflammation
L9 1476 L2 AND INFLAMMATION

=> s l9 and "BSF-3"
L10 0 L9 AND "BSF-3"

=> s l2 and "NNT-1"
L11 0 L2 AND "NNT-1"

=> s senaldi g?/au
L12 413 SENALDI G?/AU

=> s l12 and NNT 1 inhibitor
L13 1 L12 AND NNT 1 INHIBITOR

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L12 ANSWER 1 OF 413 MEDLINE
2002165212 Document Number: 21895095. PubMed ID: 11897629. rHuKGF
ameliorates symptoms in DSS and CD4(+)CD45RB(Hi) T cell transfer mouse
models of inflammatory bowel disease. Byrne Fergus R; Farrell Catherine L;
Aranda Richard; Rex Karen L; Scully Sheila; Brown Heather L; Flores Silvia
A; Gu Li H; Danilenko Dimitry M; Lacey David L; Ziegler Thomas R;
Senaldi Giorgio. (Department of Pharmacology, Amgen, Thousand
Oaks, California 91320, USA.. fbyrne@amgen.com) . AMERICAN JOURNAL OF
PHYSIOLOGY. GASTROINTESTINAL AND LIVER PHYSIOLOGY, (2002 Apr) 282 (4)
G690-701. Journal code: 100901227. ISSN: 0193-1857. Pub. country: United
States. Language: English.

AB There is an acute need for effective therapy for inflammatory bowel
disease (IBD), particularly at the level of repair of the damaged
epithelium. We evaluated the efficacy of recombinant human keratinocyte
growth factor (rHuKGF) in both the dextran sodium sulfate (DSS) and the
CD4(+)CD45RB(Hi) T cell transfer models of IBD. Disease was induced either
by the ad libitum administration to normal mice of 4% DSS in the drinking
water or by the injection of 4×10^5 CD4(+)CD45RB(Hi) T cells into
immunodeficient scid/scid mice. rHuKGF was administered by subcutaneous
injection at doses of 1.0 or 3.0 mg/kg in both preventative and
therapeutic regimens during both studies. rHuKGF significantly improved
survival and body weight loss in the DSS model in both preventative and
therapeutic dosing regimens. It also improved diarrhea, hematochezia, and
hematological parameters, as well as large intestine histopathology. In
the T cell transfer model, rHuKGF improved body weight loss, diarrhea, and
levels of serum amyloid A, as well as large intestine histopathology. In
both models of IBD, the colonic levels of intestinal trefoil factor (ITF)
were elevated by the disease state and further elevated by treatment with
rHuKGF. These data suggest that rHuKGF may prove useful in the clinical
management of IBD and its effects are likely mediated by its ability to
locally increase the levels of ITF.

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 L7 0 S L2 AND NEUTROPHIN 1 INHIBITOR
 L8 0 S L2 AND B CELL STIMULATING FACTOR 3
 L9 1476 S L2 AND INFLAMMATION
 L10 0 S L9 AND "BSF-3"
 L11 0 S L2 AND "NNT-1"
 L12 413 S SENALDI G?/AU
 L13 1 S L12 AND NNT 1 INHIBITOR

=> s l12 and antibody
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 L16 3 DUP REMOVE L15 (0 DUPLICATES REMOVED)

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L16 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
 2002:157624 Document No. 136:215409 Anti-novel neurotrophic factor 1 (
NNT-1) antibodies and soluble **NNT-1**
 1 receptor for treating IgE-related disease. **Senaldi,**
Giorgio (Amgen Inc., USA). PCT Int. Appl. WO 2002015977 A2 20020228,
 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR,
 BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB,
 GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
 LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT,
 RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
 ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG,
 CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR,
 NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION:
 WO 2001-US25906 20010817. PRIORITY: US 2000-PV226436 20000818; US
 2001-931704 20010816.

AB Disclosed are novel methods and compns. for diagnosing and treating
 IgE-related diseases using **NNT-1** inhibitors. The
NNT-1 inhibitors include antagonistic anti-**NNT**
-1 antibodies, chimeric or humanized
antibodies, and CDR-grafted **antibodies** or fragments, as
 well as sol. **NNT-1** receptor. The IgE-related diseases
 include allergy, allergic rhinitis, eczema, dermatitis, pollinosis,
 asthma, and others. In one embodiment, the present invention relates to a
 method of treating IgE-related diseases using a selective binding agent to
NNT-1. In another embodiment, the present invention
 relates to a method of treating IgE-related diseases using an **NNT**
-1 expression modulator. Methods of modulating IgE levels, and
 of diagnosing, preventing and/or treating certain types of allergic
 diseases using **NNT-1** inhibitors are also disclosed.

L16 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 2002:186711 Document No.: PREV200200186711. B-cell stimulating factor-3/novel
 neurotrophin-1: A novel myeloma cell growth factor of the GP130-family.
 Burger, Renate (1); Bakker, Frank (1); Guenther, Andreas (1); Baum,
 Wolfgang (1); **Senaldi, Giorgio**; Gramatzki, Martin (1). (1)
 Division of Hematology/Oncology, Department of Medicine III, University of
 Erlangen-Nuernberg, Erlangen Germany. Blood, (November 16, 2001) Vol. 98,
 No. 11 Part 1, pp. 373a. <http://www.bloodjournal.org/>. print. Meeting

Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1
Orlando, Florida, USA December 07-11, 2001 ISSN: 0006-4971. Language:
English.

- AB Novel neurotrophin-1 (**NNT-1**)/B cell-stimulating factor-3 (BSF-3), also named cardiotrophin-like cytokine (CLC), was recently cloned and characterized to belong to the class of interleukin (IL)-6-type cytokines. The members of this family, namely IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF) and cardiotrophin-1 (CT-1), all use the gp130 signaling subunit as a part of their receptor complexes. Along with gp130, the cellular receptor for BSF-3 also includes the LIF receptor (LIFR) beta-chain. BSF-3, similar to IL-6, possesses B cell-stimulating capability. Since IL-6 is a major growth factor for malignant plasma cells, BSF-3 could also play a role in multiple myeloma. We used a gp130/LIFR expressing subline of the IL-6-dependent human plasma cell line INA-6 to evaluate BSF-3 activity and to characterize the intracellular signaling pathways that are induced by BSF-3. Growth of the human plasmacytoma cell line INA-6/Tu11 is dependent on IL-6 and the cells also respond to other cytokines of the gp130-family. Stimulation of Tu11 cells with human recombinant BSF-3 significantly induced cell proliferation as measured by (3H)thymidine uptake. BSF-3 induced proliferation was almost completely blocked by anti-gp130 monoclonal **antibodies**. Interestingly, an anti-gp130 **antibody** that specifically neutralizes CNTF activity, significantly reduced BSF-3 induced DNA synthesis. As with the other gp130-cytokines, the tyrosine kinase inhibitor tyrphostin AG490 blocked BSF-3 induced proliferation in a dose-dependent manner indicating the involvement of Jak kinases in signal transduction. It could be shown by immunoblotting that STAT3 is phosphorylated on tyrosine residues upon stimulation with BSF-3. For the first time, it can be demonstrated that BSF-3, a novel member of the gp130-family of cytokines, promotes plasmacytoma cell growth and activates the Jak/STAT signaling pathway. The results also indicate that the physiological CNTF receptor may participate in BSF-3 binding on human plasma cells. BSF-3 is strongly expressed in secondary lymph organs and in bone tissue, and may play a role in the pathophysiology of multiple myeloma, thereby acting in a paracrine or even autocrine manner.

L16 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2002 ACS

1999:684546 Document No. 132:22000 Novel neurotrophin-1/B cell-stimulating factor-3: a cytokine of the IL-6 family. **Senaldi, Giorgio**; Varnum, Brian C.; Sarmiento, Ulla; Starnes, Charlie; Lile, Jackson; Scully, Sheila; Guo, Jane; Elliott, Gary; McNinch, Jennifer; Shaklee, Christine L.; Freeman, Daniel; Manu, Frank; Simonet, W. Scott; Boone, Thomas; Chang, Ming-Shi (Amgen Inc., Thousand Oaks, CA, 91320, USA). Proceedings of the National Academy of Sciences of the United States of America, 96(20), 11458-11463 (English) 1999. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

- AB The authors have identified a cytokine of the IL-6 family and named it novel neurotrophin-1/B cell-stimulating factor-3 (**NNT-1**/BSF-3). **NNT-1**/BSF-3 cDNA was cloned from activated Jurkat human T cell lymphoma cells. Its sequence predicts a 225-aa protein with a 27-aa signal peptide, a mol. mass of 22 kDa in mature form, and the highest homol. to cardiotrophin-1 and ciliary neurotrophic factor. The gene for **NNT-1**/BSF-3 is on chromosome 11q13. A murine equiv. to **NNT-1**/BSF-3 also was identified, which shows 96% homol. to human **NNT-1**/BSF-3. **NNT-1**/BSF-3 mRNA is found mainly in lymph nodes and spleen. **NNT-1**/BSF-3 induces tyrosine phosphorylation of glycoprotein 130 (gp130), leukemia inhibitory factor receptor .beta., and signal transducer and activator of transcription 3 in the SK-N-MC human neuroblastoma cells. **NNT-1**/BSF-3 shows activities typical of IL-6 family members. In vitro, it supports the survival of chicken embryo motor and sympathetic neurons. In mice, it

induces serum amyloid A, potentiates the induction by IL-1 of corticosterone and IL-6, and causes body wt. loss and B cell hyperplasia with serum IgG and IgM increase. **NNT-1/BSF-3** is a gp130 activator with B-cell stimulating capability.

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